

4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-D-4628]

Risk Evaluation and Mitigation Strategies Assessment: Planning and Reporting; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry on the assessment of risk evaluation and mitigation strategies (REMS) entitled “REMS Assessment: Planning and Reporting; Draft Guidance for Industry.” The draft guidance is one of several guidance documents being developed to fulfill performance goals under the fifth authorization of the prescription drug user fee program, the Prescription Drug User Fee Act V. This draft guidance describes how to develop a REMS Assessment Plan; specifically, how the REMS program goals, objectives, and REMS design may impact the selection of metrics and data sources, which will be used to assess whether the REMS is meeting its risk mitigation goals.

The draft guidance recommends assessing the REMS using both process measures and outcome measures and provides examples of metrics by assessment categories, as well as data sources that may be utilized to evaluate the performance of the REMS. The draft guidance also discusses considerations for assessing the impact of REMS on patient access to the drug or its burden to the healthcare delivery system. Finally, this draft guidance provides recommendations

on a standardized approach for reporting REMS assessment findings to FDA using the REMS Assessment Report.

DATES: Submit either electronic or written comments on the draft guidance by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]** to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2018-D-4628 for “REMS Assessment: Planning and Reporting.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the

body of your comments and you must identify this information as “confidential.”

Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Bldg., 4th Floor, Silver Spring, MD 20993-0002, or to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Doris Auth, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 2480, Silver Spring, MD 20993-0002, 301-796-0487, Doris.Auth@fda.hhs.gov; or Stephen Ripley,

Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “REMS Assessment: Planning and Reporting.” The Food and Drug Administration Amendments Act of 2007 created section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1), which authorizes FDA to require a REMS for certain drugs if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.

REMS elements may include a medication guide, a patient package insert, and/or a communication plan. FDA may also require certain elements to assure safe use (ETASU) as part of a REMS. The ETASU can include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe use conditions. Certain REMS with ETASU may also include an implementation system through which the sponsor is able to monitor and evaluate implementation of the ETASU and work to improve their implementation. All REMS for drugs approved under a new drug application or a biologics license application must include a timetable for submission of assessments of the REMS. The timetable for submission of assessments must be, at a minimum, by 18 months, 3 years, and in the 7th year after the initial approval of the REMS. For additional information about REMS, see the guidances for industry “Format and Content of a REMS Document” (82 FR 47529, October 12, 2017) (available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs->

gen/documents/document/ucm184128.pdf), FDA's Application of Statutory Factors in Determining When a REMS Is Necessary (81 FR 64911, September 21, 2016) (available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM521504.pdf>), and Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry (80 FR 18629, April 7, 2015) (available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM441226.pdf>).

The FD&C Act requires applicants to conduct assessments to evaluate the effectiveness of the REMS. The statute specifies that the assessment for REMS must include an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified (section 505-1(g)(3) of the FD&C Act). The statute does not specifically describe how an applicant should conduct assessments. Many REMS include a goal related to knowledge, such as to inform or educate patients and health care providers about the serious risks associated with and safe use of a drug. When knowledge goals are part of a REMS, the REMS Assessment Plan generally includes, as appropriate, an evaluation of patients' and health care providers' understanding of the serious risk(s) associated with, and safe use of, the drug. Elsewhere in this issue of the *Federal Register*, FDA is announcing the availability of a draft guidance entitled "Survey Methodologies to Assess REMS Goals That Relate to Knowledge," which addresses the use of surveys to address the knowledge goal.

In addition to knowledge-related goals, REMS may include goals and objectives related to the outcomes the REMS is intended to mitigate; therefore, REMS assessments should also include elements that would indicate whether these goals and objectives are being met. REMS

assessments can also include elements to assess the burden of REMS on the health care delivery system and any unintended barriers to patient access of the drug.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "REMS Assessment: Planning and Reporting." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

II. Paperwork Reduction Act of 1995

This draft guidance refers to collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection are given under this section with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, and gathering and maintaining the data needed.

We invite comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: REMS Assessment: Planning and Reporting--OMB Control Number 0910-NEW

Description: This draft guidance provides instruction on submitting REMS Assessments to FDA. These instructions recommend that application holders submitting REMS Assessments should include the following information in each submission: (1) a cover page that includes the reporting time point, the date of the REMS Assessment Report, and the assessment reporting period. The cover page should be followed by (2) a table of contents; (3) an executive summary of the findings and conclusions; (4) an introduction section; (5) a background section, which includes the REMS goals and objectives, requirements, and materials that were in place during the assessment reporting period, a REMS history, and any pending supplements; (6) a summary of the REMS Assessment Plan as an overview in tabular format (or other format outline) and details of the assessment plan including any study protocols submitted with the assessment or references to protocols submitted prior to the REMS Assessment Report and methodology used to support REMS assessment (e.g., survey, other methodology); (7) a summary of the previous assessments, including the key results and the overall conclusions; (8) the results or summary of findings of each assessment metric, including a written summary of the data that was analyzed, key results and a description of any limitations. When appropriate, the data should be reported for the reporting period and cumulatively, and trends in performance compared to previous periods should be reported and discussed; (9) a discussion including the overall assessment of whether the REMS is meeting its goals and objectives, including the basis for that conclusion, and for REMS with ETASU, whether the burden on the healthcare delivery system is being minimized to the extent practicable, whether the ETASU are unduly burdensome on patient access to medication, and an explanation for these conclusions; (10) any proposed modifications to the REMS (e.g., to address REMS compliance issues, reduce burdens, overcome barriers to

patient access, improve efficiencies) as well as the basis for the proposed modifications; and (11) any proposed revisions to the REMS Assessment Plan if additional information is needed to make a determination that the goal of the REMS is being met, or if there are aspects of the REMS that are no longer necessary to assess.

We estimate the burden of the information collection as follows:

Table 1.--Estimated Annual Reporting Burden¹

Guidance for industry on REMS Assessment: Planning and Reporting	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response (hours)	Total Hours
REMS Assessments Submissions	47	1	47	162.5	7,638

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

There are currently 76 approved REMS programs. Based on a current review of REMS assessment submission data and anticipating a similar number of future submissions, we estimate that there will be 47 REMS Assessment submissions annually. We also estimate that it will take an application holder 162.5 hours to prepare and submit each REMS Assessment (“Average Burden per Response” in table 1) in accordance with recommendations found in the guidance.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, or <https://www.regulations.gov>.

Dated: January 16, 2019.

Leslie Kux,

Associate Commissioner for Policy.

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